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Scale Specific and Scale Independent Measures of Heart Rate Variability as Risk Indicators

Y. ASHKENAZY^{1,2(*)}, M. LEWKOWICZ^{3,1}, J. LEVITAN^{3,1,4}, S. HAVLIN^{1,2}, K. SAERMARK⁴,
H. MOELGAARD⁵, P.E. BLOCH THOMSEN⁶, M. MOLLER⁷, U. HINTZE⁷, AND H.V. HUIKURI⁸

¹ *Dept. of Physics, Bar-Ilan University, Ramat-Gan, Israel*

² *Gonda Goldschmied Center, Bar-Ilan University, Ramat-Gan, Israel*

³ *Dept. of Physics, College of Judea and Samaria, Ariel, Israel*

⁴ *Dept. of Physics, The Technical University of Denmark, Lyngby, Denmark*

⁵ *Dept. of Cardiology, Skejby Sygehus, Aarhus University Hospital, Aarhus, Denmark*

⁶ *Dept of Cardiology, Amtssygehuset i Gentofte, Copenhagen University Hospital, Denmark*

⁷ *Inst. Clin. Res. Cardiology, University of Southern Denmark, Odense, Denmark*

⁸ *Div. Cardiology, Dept. of Medicine, University of Oulu, Finland*

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Abstract. – We study the Heart Rate Variability (HRV) using scale specific variance and scaling exponents as measures of healthy and cardiac impaired individuals. Our results show that the variance and the scaling exponent are uncorrelated. We find that the variance measure at certain scales is well suited to separate healthy subjects from heart patients. However, for cumulative survival probability the scaling exponents outperform the variance measure. Our risk study is based on a database containing recordings from 428 individuals after myocardial infarct (MI) and on database containing 105 healthy subjects and 11 heart patients. The results have been obtained by applying three recently developed methods (DFA - Detrended Fluctuation Analysis, WAV - Multiresolution Wavelet Analysis, and DTS - Detrended Time Series analysis) which are shown to be highly correlated.

The study of heart rate variability (HRV) has been in use for the last two decades as part of clinical and prognostic work; international guidelines for evaluating conventional HRV-parameters do exist [1]. The conventional parameters are power spectra [2] and standard deviation [3, 4]. Recently three new methods of analyzing heart interbeat interval (RR) time series have been developed, all of them showing signs of improved diagnostic performance. The three methods are: Detrended Fluctuation Analysis (DFA) [5, 6, 7, 8, 9], Multiresolution

(*) Email:ashkenaz@argento.bu.edu

Wavelet Analysis (WAV) [10, 11, 12, 13, 14, 15] and Detrended Time Series Analysis (DTS) [16]. The question which method and which measure yield better separation between cardiac impaired and healthy subjects has been recently debated [13, 14, 17].

In this Letter we show that variance, which is a scale specific measure, is well suited to separate between healthy subjects and heart patients. However, for the myocardial infarct (MI) group the scaling exponent, which is a scale independent measure, serves as a better risk indicator. Moreover, we show that the three above mentioned methods for both variance and scaling exponent, are correlated and converge to similar results while the variance and the scaling exponent are uncorrelated.

In our study we use two groups, the MI group, containing 428 heart patients after MI and a control group, consisting of 105 healthy individuals and 11 cardiac impaired patients (9 diabetic patients, one diabetic patient after myocardial infarct, and one heart transplanted patient). Our analysis is based on 24 hour heart interbeat interval time series [18]. We applied the following methods.

The DFA Method. The detrended fluctuation analysis was proposed by Peng *et al* [5]. This method avoids spurious detection of correlations that are artifacts of nonstationarity. The interbeat interval time series is integrated after subtracting the global average and then divided into windows of equal length, n . In each window the data are fitted with a least square straight line which represents the local trend in that window. The integrated time series is detrended by subtracting the local trend in each window. The root mean square fluctuation, the standard deviation $\sigma_{\text{dfa}}(n)$ of the integrated and detrended time series is calculated for different scales (window sizes); the standard deviation can be characterized by a scaling exponent α_{dfa} , defined as $\sigma(n) \sim n^\alpha$.

The WAV Method. In the WAV method [13, 14, 19] one finds the wavelet coefficients $W_{m,j}$, where m is a ‘scale parameter’ and j is a ‘position’ parameter (the scale m is related to the number of data points in the window by $n = 2^m$ [18]), by means of a wavelet transform. The standard deviation $\sigma_{\text{wav}}(m)$ of the wavelet coefficients $W_{m,j}$ across the parameter j is used as a parameter to separate healthy from sick subjects. The corresponding scaling exponents is denoted by α_{wav} .

The DTS Method. The detrended time series method was suggested in [16]. In this method one detrends the RR time series by subtracting the local average in a running window from the original time series, resulting in a locally detrended time series. The standard deviation σ_{dts} is calculated for various window scales with a scaling exponent α_{dts} .

The first suggestion to use a scale independent measure of the HRV as a separation parameter was by Peng *et al* [5] who found that a critical value of the DFA scaling exponent α_{dfa} can distinguish between healthy individuals and heart patients. Thurner *et al* [13] used the scale specific WAV variance σ_{wav} in order to better separate the same two groups. The debate, which method performs better was continued in two recent Letters [14, 17]. Later on, another independent study on different database [19] yielded a better separation using the scale specific σ_{wav} measure.

In Fig. 1 we compare the conventional measures for HRV for the control group: the variance (which is calculated for a fixed scale) for the DTS and WAV method (σ_{dts} and σ_{wav}) and the scaling exponent (which is calculated for a range of scales) for the DFA method (α_{dfa}). One notes that the scale specific measures, σ_{dts} and σ_{wav} , yield a nearly perfect separation between healthy and sick subjects (the p value of the student t-test is less than 10^{-14}), compared with the scale independent measure α_{dfa} which yields less pronounced separation (p value of the student t-test is less than 10^{-4}).

This outcome is reversed when we applied the measures on the MI group. Since we have no diagnostics on this group, but rather do know the follow-up history for 328 individuals

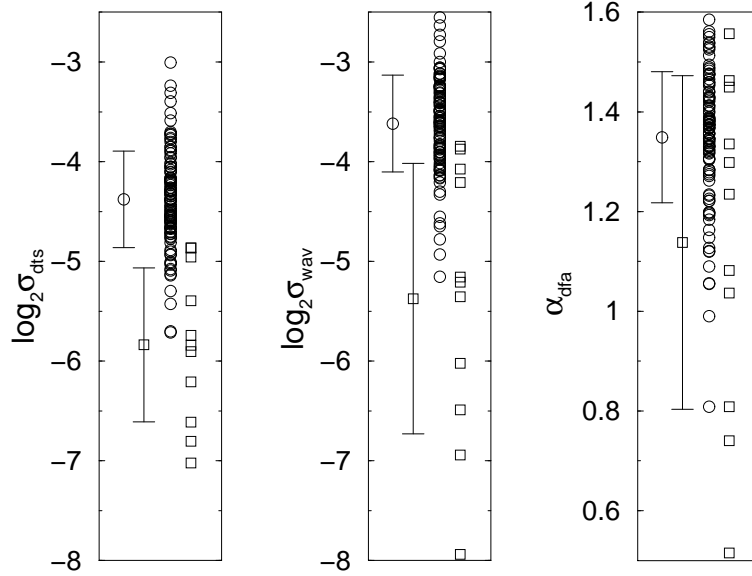


Fig. 1. – A comparison between different HRV methods (DTS, WAV, and DFA). The 105 healthy subjects are denoted by \circ , while 11 heart patients are denoted by \square . The error bars indicate the average ± 1 standard deviation of each group. The σ_{dts} is calculated at scale $m = 8$, σ_{wav} at scale $m = 4$, and α_{dfa} for scales $1 \leq m \leq 4$; it was previously reported in the literature that this choice of parameters yields the best separation between healthy group and heart failure group [5, 13, 16].

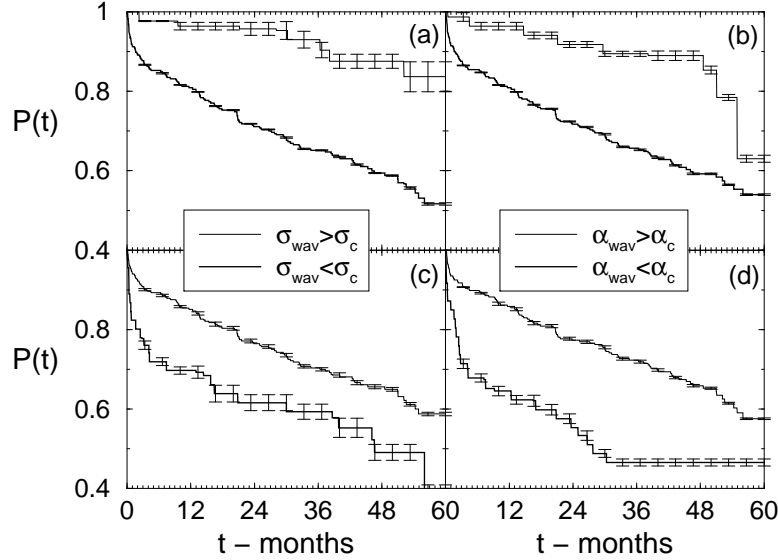


Fig. 2. – Cumulative survival probability curves using the WAV method. We divide the entire group of 328 individuals into two groups according to a critical value σ_c or α_c . The survival curves shown in the figure are the average of 10 different survival curves, with close critical values. In the upper panel we average over the 40-50 largest parameter values and in the lower panel we average over the 40-50 smallest parameter values. We perform this average procedure in order to check the sensitivity to the critical value. The error bars indicate the standard deviation from the average. The average critical values are (a) $\langle \log_2 \sigma_c \rangle = -3.749$, (b) $\langle \alpha_c \rangle = 0.68$, (c) $\langle \log_2 \sigma_c \rangle = -5.485$, and (d) $\langle \alpha_c \rangle = 0.135$.

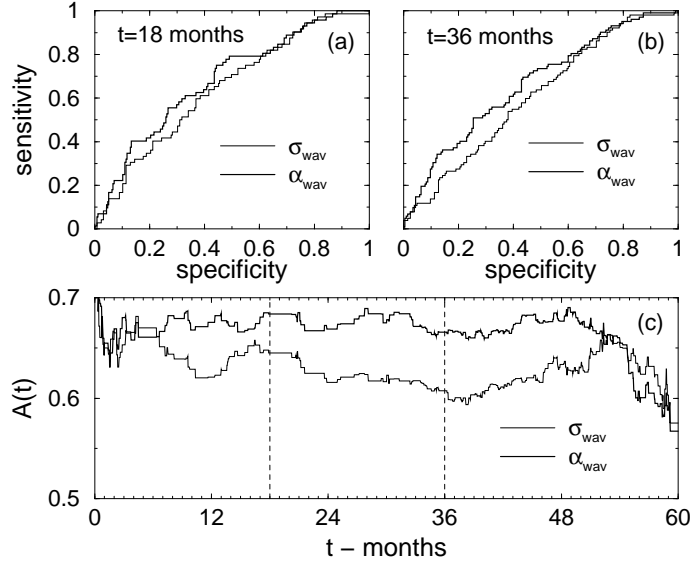


Fig. 3. – The ROC curves (sensitivity vs specificity) of the scale specific, σ_{wav} , and scale independent, α_{wav} , measures. (a) $t = 18$ months, (b) $t = 36$ months, and (c) $A(t)$ — the area under the ROC curve — as a function of time. In all figures the scale independent curve is located above the scale specific curve. Thus, the scale-independent measure is more suitable for prognostic purposes.

from the total 428 individuals of the larger group, we investigate the survival probability of these subjects as expressed through the so-called survival curve [20]. In these curves one divides the entire group by means of a specific value of the σ or α measure, called the critical value σ_c or α_c . For each subgroup we calculate the cumulative survival probability given by $P(t + \Delta t) = P(t)[1 - \Delta N/N(t)]$, where $P(t)$ is the probability to survive up to t days after the ECG recording, $N(t)$ denotes the number of individuals alive at t days after the examination, and ΔN is the number of individuals who died during the time interval Δt . In Fig. 2 we show a comparison of survival curves where the separating measure in figures (a) and (c) is the critical standard deviation σ_c and in figures (b) and (d) the critical scaling exponent α_c . Individuals with $\sigma > \sigma_c$ (or $\alpha > \alpha_c$) belong to the subgroup with the higher survival probability; the upper panel extracts the subgroup with a high survival probability, whereas the lower panel extracts the subgroup with a low survival probability. This comparison shows that the scale independent scaling exponent α serves as a better prognostic predictor than the scale specific variance σ (although Fig. 2a and b are similar the survival curves of Fig. 2d are more separated than the survival curves of Fig. 2c).

In Fig. 2 we use the σ and α measures obtained through the WAV method. However, as we show below all three methods discussed above are highly correlated and no significant difference is noticeable in the survival curves when using DFA and DTS measures.

The advantage of the scale independent measure α over the scale specific measure σ is also shown in Fig. 3. Here we scan the possible critical values by the Receiver Operating Characteristic (ROC) analysis [21]; this analysis is usually used as a medical diagnostic test and also was the basic diagnostic test of Ref. [17]. The idea of the ROC method is to compare the result of medical test (positive or negative) with the clinical status of the patient (with or without disease). The efficiency of the medical test is judged on the basis of its sensitivity (the proportion of diseased patients correctly identified) and its specificity (the proportion of

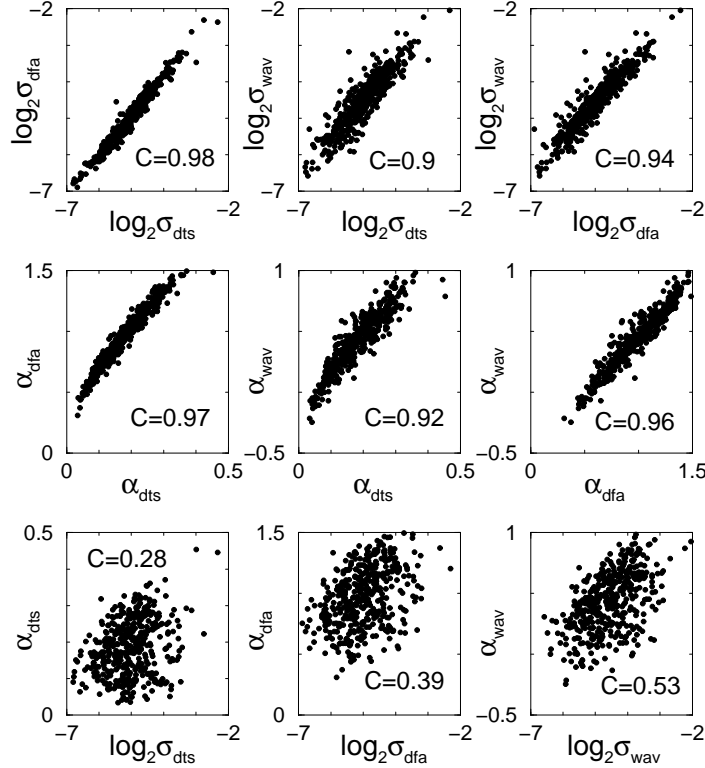


Fig. 4. – A comparison between different HRV methods using 428 individuals. The value C in each figure indicates the cross-correlation value between the different measures [22]. Upper panel - σ measure versus σ measure; middle panel - α measure versus α measure; lower panel - σ measure versus α measure. The σ_{dfa} and σ_{wav} is calculated at $m = 4$, σ_{dts} at $m = 8$; α_{dfa} and α_{wav} is calculated for $m = 1$ to 4, α_{dts} for $m = 1$ to 8.

healthy patients correctly identified). The ROC curve is a graphical presentation of sensitivity versus specificity as a critical parameter is swept. In our case the patient status is determined according to its mortality (death or survival up to time t) and according to its mortality prediction (a patient with parameter value smallest than the critical value is predicted to die while a patient with a parameter value larger than the critical value is predicted to survive). In Fig. 3a and b we present two examples of the ROC curves in different times (18 months and 36 months). In both cases the ROC of the scale independent (α_{wav}) curve is located above the scale specific (σ_{wav}) curve; the larger the area under the ROC curve is, the better is the parameter. In the ideal case a patient with small parameter value will die before the patient with higher parameter value. In this case the area under the ROC curve will be 1. On the other hand, when there is no relation between the value of the parameter and the mortality of the patient the area under the ROC curve will be $1/2$. In Fig. 3c we show the area under the ROC curves as a function of time ($A(t)$). The scale independent (α_{wav}) curve is located above the scale specific (σ_{wav}) curve. Thus, the scale independent measure α_{wav} is more suitable for prognosis.

In order to investigate if the three methods we use are correlated, we apply them on the larger MI group consisting of 428 subjects. The top panel of Fig. 4 shows that the variances (the scale specific measure) of the three methods are highly correlated. This is also true

for the scaling exponents (the scale independent measure, middle panel). These comparisons indicate that indeed the various methods yield the same results in terms of variance and scaling exponents. On the other hand, the lower panel of Fig. 4 shows that the scale specific variance and the scale independent scaling exponent are uncorrelated for the DTS and DFA methods and are only faintly correlated for the WAV method.

From this we conclude that the α and σ measures characterize the interbeat interval series in different ways; the variance, which is a measure in the time domain (and thus is almost invariant to shuffling [13]), performs better as a diagnostic tool, while the scaling exponent, which is a measure in the frequency domain, depends on the order of events and performs better as a prognostic tool. Thus we suggest that the scale specific variance reflects changes in either the sympathetic or the parasympathetic activities of the neuro-autonomic nervous system [23] which affect the cardiac ability of contraction; the scale specific variance may hint on the instant condition of the physical properties of the heart. From the above we also suggest that the scale independent scaling exponent characterize the memory interplay of the two competing branches of the autonomic nervous system (the sympathetic and the parasympathetic systems) and is thus an expression of the underlying mechanism of heart regulation (which influences the conventional power spectrum [2])[24].

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- [22] Given two series ($\{x_i\}$ and $\{y_i\}$) with the same length the cross-correlation value is $C = \frac{\sum[(x_i - \langle x \rangle)(y_i - \langle y \rangle)]}{\sqrt{\sum(x_i - \langle x \rangle)^2 \sum(y_i - \langle y \rangle)^2}}$, where $\langle \dots \rangle$ indicates the average of the series.
- [23] The sympathetic/parasympathetic system is the system which increases/decreases the heart rate.
- [24] An increase/decrease in one of the activities is usually compensated by a decrease/increase in the other activity. In cardiac failure the regulation between the two activities breaks down.